said lipidized antibdody is capable of transvascular transport, organ uptake or intracellular localization.

20. (Amended) A [composition comprising a] lipidized antibody, wherein said lipidized antibody is linked to a [diagnostic reporter] label selected from the group consisting of radionuclides, enzymes, enzyme substrates, enzyme inhibitors, ligands, radiocontrast agents and metal chelates, wherein a lipid substituent is covalently linked to the antibody by a covalent linkage of at least one lipoamine residue to a carbohydrate side chain to produce said [a] lipidized antibody and wherein said lipidized antibody is capable of transvascular transport, organ uptake or intracellular localization.

22. (Amended) A composition of claim 21 [22], wherein the antibody binds to the HIV-1 Tat protein intracellularly in HIV-infected human cells.

REMARKS

Applicants wish to thank Examiner Schwadron for the telephonic interview held on October 27, 1998 in which the three related, copending patent applications (*i.e.*, U.S. Patent Applications Serial Nos. 08/483,944, 08/482,116 and the present case, *i.e.* 08/973,576) were discussed. During this interview, a number of issues were clarified and a number of amendments were proposed which have helped Applicant to more fully address the concerns of the Examiner. Applicant thanks Examiner Schwadron for his time.

Claims 1-23 are pending in the above-referenced patent application; claims 1-23 are currently under examination. In order to expedite prosecution of the present case, claims 1, 9, 14, 19, and 20 have been amended to more specifically recite that the lipidized protein (claims 1 and 14) or the lipidized antibody (claims 9, 19 and 20) is capable of transvascular transport, organ uptake or intracellular localization. Support for this amendment can be found throughout the specification and, in particular, at page 5, lines 24-28, page 7, lines 32-37, page 16, lines 13-16, *etc.* Accordingly, no new matter has been introduced by this amendment. Moreover, in order to expedite prosecution, claims 14 and 19 have been amended to more specifically recite a composition comprising a lipidized protein and a lipidized antibody,

respectively, and a pharmaceutically acceptable carrier. Support for this amendment can be found throughout the specification and, thus, no new matter has been introduced. In addition, claim 20 has been amended, in part, to recite "a lipidized antibody, wherein said lipidized antibody is linked to a label selected from the group consisting of radionuclides, enzymes, enzyme substrates, enzyme inhibitors, ligands, radiocontrast agents and metal chelates. . . ." Support for this amendment can be found, for example, at page 29, lines 2-8 and, thus, no new matter has been introduced. Further, claim 22 has been amended so that it properly depends from claim 21. No new matter has been introduced. Finally, claim 23 has been canceled without prejudice.

In response to the Examiner's notification that the oath or declaration is defective, Applicant submits concurrently herewith a substitute declaration that claims priority to copending U.S. Patent Application Serial No. 08/482,116, filed June 7, 1995, and U.S. Patent Application Serial No. 07/912,453, filed June 13, 1992, now abandoned. In view of the substitute declaration and the amendment to the specification, Applicant respectfully submits that the Examiner's concern is overcome.

The Draftsperson has objected to the figures submitted with the original application for the reasons set forth in PTO FORM 948. Applicant respectfully requests that the Draftsperson's objections to the figures be held in abeyance until issuance of a formal Notice of Allowance. At that time, Applicant will file formal drawings which will overcome the stated objections.

In response to the Examiner's notification that the present case fails to comply with the requirements of 37 C.F.R. § 1.821-§ 1.825, Applicant submits concurrently herewith in a separate paper a "Communication Under 37 C.F.R. § 1.821-§ 1.825 and Amendment" which fully complies with the requirements of 37 C.F.R. § 1.821-§ 1.825. If the Examiner requires any additional information the relating to this Sequence Listing, Applicant will be more than happy to provide the Examiner with this information.

Claim 23 is provisionally rejected under 35 U.S.C. as claiming the same invention as that of claim 23 of copending U.S. Patent Application Serial No. 08/482,116. Claims 14-23 are provisionally rejected under the judicially created doctrine of obviousness-

type double patenting as being unpatentable over claims 1, 2 4-12, 24 and 29-33 of copending U.S. Patent Application Serial No. 08/483,944. Claims 1-22 and 23 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-23 and claims 1-22, respectively, of copending U.S. Patent Application Serial No. 08/482,116. Claims 1-8 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly being nonenabled. Claims 14-22 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Claims 1-23 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Kabanov, *et al.* and Kabanov, *et al.* in view of Bischofberger, *et al.*, Rodwell, *et al.* and prior art disclosed in the specification (page 30, lines 12-15). Claims 1-3, 7, 8, 14, 15, 19, 20 and 23 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Horan, *et al.* (U.S. Patent No. 5,665,328). Claims 1-23 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Malfroy-Camine (WO 94/01131). Finally, claims 1-8, 14, 15, 19, 20 and 23 remain rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Horan, *et al.* in view of Bischofberger, *et al.* and prior art disclosed in the specification (page 30, lines 12-15). For the reasons set forth herein, each of the Examiner's rejections is overcome.

REJECTION UNDER 35 U.S.C. § 101:

Claim 23 is provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as that of claim 23 of copending U.S. Patent Application Serial No. 08/482,116.

In order to expedite prosecution of the present case, claim 23 has been canceled. In view of this amendment, the Examiner's provisional rejection has been rendered moot. Accordingly, Applicant urges the Examiner to withdraw the provisional rejection of claim 23 under 35 U.S.C. § 101.

OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTION:

Claims 14-23 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2 4-12, 24 and 29-33 of copending U.S. Patent Application Serial No. 08/483,944. In addition, claims 1-22 and 23 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-23 and claims 1-22, respectively, of copending

U.S. Patent Application Serial No. 08/482,116. The Examiner has indicated that these provisional rejections can be overcome by timely filing a Terminal Disclaimer.

Applicant acknowledges that copending Patent Applications Serial Nos. 08/438,944 and 08/482,116 have claims that are similar to those in the present case. However, Applicant is entitled to at least one patent relating to the claimed invention and, thus, upon withdrawal of the other outstanding rejections/objections in the present case, Applicants will cancel the conflicting claims in copending U.S. Patent Applications Serial Nos. 08/438,944 and 08/482,116 or, alternatively, they will file a Terminal Disclaimer. As such, Applicants respectfully request that this provisional rejection be held in abeyance until the other outstanding objections/rejections have been withdrawn.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH:

Claims 1-8 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly being nonenabled. In making this objection/rejection, the Examiner has alleged that the specification does not teach how the characteristics of a protein are modified.

Applicant respectfully disagrees and, in doing so, respectfully submits that the specification does, in fact, teach how to modify the characteristics of a protein. For instance, the specification teaches that by lipidizing a protein, one can enhance the transvascular transport and/or intracellular localization of the protein. However, in order to expedite prosecution of the present case, Applicant has amended claim 1 to set forth "a method of making a lipidized protein." In view of the amendment to claim 1, the Examiner's objection/rejection is rendered moot. Accordingly, Applicant urges the Examiner to withdraw this portion of the objection/rejection under 35 U.S.C. § 112, first paragraph.

REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH:

Claims 14-22 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention. Each of the Examiner's concerns and, in turn, Applicant's responses to those concerns are set forth hereinbelow.

a. The Examiner has alleged that claims 14-22 are indefinite because they read on compositions, but claim compounds. The Examiner has further stated that the claims need to recite additional ingredients (*e.g.*, a buffer) that would render these claims compositions and not compounds.

In order to expedite prosecution of the present case, claims 14 and 19 have been amended to set forth that the lipidized protein and lipidized antibody, respectively, are present in a pharmaceutically acceptable carrier. In addition, claim 20 has been amended to recite a compound and not a composition. In view of the amendments to claims 14, 19 and 20, the Examiner's rejection is rendered moot. Accordingly, Applicant urges the Examiner to withdraw this portion of the § 112, second paragraph, rejection.

b. The Examiner has alleged that claim 19 is indefinite as a result of the recitation of "prophylaxis" because it is unclear what this term encompasses. Applicant respectfully submits that the meaning of the term "prophylaxis" is known to those of skill in the art. However, in order to expedite prosecution of the present case, claim 19 has been amended to delete any reference to prophylaxis. In view of the amendment to claim 19, the Examiner's rejection is rendered moot. Accordingly, Applicant urges the Examiner to withdraw this portion of the § 112, second paragraph, rejection.

c. The Examiner has alleged that claim 20 is indefinite in the recitation of "diagnostic reporter" because it is unclear what this term encompasses.

In order to expedite prosecution of the present case, claim 20 has been amended, in part, to recite "a lipidized antibody, wherein said lipidized antibody is linked to a label selected from the group consisting of radionuclides, enzymes, enzyme substrates, enzyme inhibitors, ligands, radiocontrast agents and metal chelates." Support for this amendment can be found, for example, at page 29, lines 2-8 and, thus, no new matter has been introduced. In view of the amendment to claim 20, the Examiner's rejection is rendered moot. Accordingly, Applicant urges the Examiner to withdraw this portion of the rejection under § 112, second paragraph.

d. The Examiner has alleged that claim 22 is indefinite in that it is a dependent claim that depends on itself.

In order to expedite prosecution of the present case, claim 22 has been amended so that it properly depends from claim 21 and not claim 22. In view of the amendment to claim 22, the Examiner's rejection is rendered moot. Accordingly, Applicant urges the Examiner to withdraw this portion of the rejection under § 112, second paragraph.

REJECTION UNDER 35 U.S.C. § 103:

b. Rejection of Claims 1-23 over Kabanov, et al. and Kabanov, et al. in view of Bischofberger, et al., Rodwell, et al. and prior art disclosed in the specification

Claims 1-23 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Kabanov, *et al.* and Kabanov, *et al.* in view of Bischofberger, *et al.*, Rodwell, *et al.* and prior art disclosed in the specification (page 30, lines 12-15). As amended, ***all*** of the pending claims are directed to (1) a lipidized protein (*e.g.*, a lipidized antibody) that is a protein (*e.g.*, an antibody) covalently linked to a lipid through a carbohydrate moiety; and (2) a lipidized protein (*e.g.*, a lipidized antibody) that is capable of transvascular transport, organ uptake or intracellular localization. For the reasons set forth herein, the presently claimed lipidized proteins are ***not*** obvious over the prior art of record.

In support of the nonobviousness of the presently claimed lipidized proteins, Applicant submits concurrently herewith a copy of a signed declaration of Dr. Bernard Malfroy-Camine, the named inventor of the above-referenced patent application, which is being filed in related, copending U.S. Patent Application Serial No. 08/482,116, wherein the Examiner has made the same rejection.

Kabanov, *et al.* is cited by the Examiner as disclosing lipidized antibodies and that such antibodies can "translocate across lipid membranes and penetrate intact cells." The Examiner acknowledges that Kabanov, *et al.* do ***not*** teach that the lipidized proteins comprise a polypeptide covalently linked to a lipid through a carbohydrate moiety. Instead, as explained by Dr. Malfroy-Camine in his declaration, Kabanov, *et al.* teach a random process for

lipidating an antibody. Kabanov, *et al.*, in essence, put lipids randomly on the antibody in such a way that the whole surface of the antibody is lipidated. As pointed out by Dr. Malfroy-Camine, this method really corresponds to "covalent liposomes" and results in a decreased affinity of the antibody for the antigen. In contrast, in the presently claimed lipidated proteins, lipids are put ***only*** on the carbohydrate moieties of the protein. As such, as explained by Dr. Malfroy-Camine, even though the lipidized antibodies of Kabanov, *et al.* may be capable of translocating across lipid membranes and penetrating intact cells, they are ***structurally different*** from the claimed lipidized proteins because they are ***not*** "lipidated protein, wherein the protein or antibody is covalently linked to the lipid through a carbohydrate moiety" as is required by ***all*** of the pending claims.

Rodwell, *et al.* is cited by the Examiner as disclosing that an amino containing compound can be attached to antibodies by oxidation of antibody saccharides to aldehydes which can react with amine containing compounds. However, the teachings of Rodwell, *et al.* ***cannot*** be looked out in a vacuum or in combination with Kabanov, *et al.* or Bischofberger, *et al.* alone. Instead, the Federal Circuit in *Dow Chemical Co.*, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988, stated:

> In determining whether such a suggestion [of obviousness] can be fairly gleaned from the prior art, ***the full field of the invention must be considered***: for the person of ordinary skill is charged with knowledge of the entire body of technological literature, ***including that which might lead away from the claimed invention***. . . . Evidence that supports, rather than negates, patentability must be fairly considered.

5 U.S.P.Q.2d at 1531-1532 (citations omitted; emphasis added). As such, the teachings of Rodwell, *et al.* must be looked out in combination with the teachings of Kabanov, *et al.*, Bischofberger, *et al.* ***and*** Horan, *et al.* The Examiner ***cannot*** dismiss the teachings of Horan, *et al.* simply by stating, for example, that the Horan, *et al.* reference is not cited in this rejection. As mandated by the Federal Circuit in *Dow Chemical Co.*, the full field of the invention must be considered, including that which might lead away from the claimed invention.

As point out by the Examiner in the Office Action, one of the major purposes of the present invention is to "deliver proteins intracellularly." Again, all of the pending claims have been amended to specifically recite (1) that the lipidized protein (*e.g.*, a lipidized antibody) is a protein (*e.g.*, an antibody) that is covalently linked to a lipid through a carbohydrate moiety, and (2) that the lipidated proteins are capable of transvascular transport, organ uptake and intracellular localization. However, looking at the teachings of Kabanov, *et al.*, Rodwell, *et al.* and Horan, *et al.*, it would not have been obvious to do this by lipidating proteins in a controlled manner so that the lipids are put only on the carbohydrate moieties of the protein. Rodwell, *et al.* may teach that an amino containing compound can be attached to antibodies by oxidation of antibody saccharides to aldehydes which can react with amine containing compounds. However, as explained by Dr. Malfroy-Camine, when the teachings of Rodwell, *et al.* are looked at in combination with ***both*** Kabanov, *et al.* ***and*** Horan, *et al.*, one of skill in the art would have thought that if one lipidates a proteins in a controlled manner so that the lipids are put ***only*** on the carbohydrate moieties of the protein, the resulting lipidated protein would bind to and embed in the membrane.

In fact, as pointed out by the Examiner in the Office Action, Horan, *et al.* did exactly this and, in doing so, they found that the resulting lipidated proteins bind to and are embedded in the membrane. Again, Horan, *et al.* explicitly state that the compounds of their invention have "a lipophilic nature which allows them to become ***embedded*** into the plasma membrane of the cell and ***remain there*** in a stable manner" (*see*, column 20, lines 17-20, of Horan, *et al.*). During the telephonic interview, the Examiner indicated that Horan, *et al.* teach that "a specific type of lipidized antibody" localizes to the lipid membrane, but that not all of the lipidized antibodies disclosed in Horan, *et al.* will localize to the lipid membrane. However, as explained by Dr. Malfroy-Camine in his declaration, the Examiner has ***failed*** to point to any teaching or suggestion in Horan, *et al.*, or any of the other cited references, that would lead one of skill in the art to believe that the remainder of the lipidated antibodies disclosed by Horan, *et al.* would be capable of transvascular transport, organ uptake and intracellular localization. Horan, *et al.* do not even mention transvascular, transport, organ uptake, intercellular localization, *etc.*

Clearly, the only teaching the Examiner has pointed to with respect to the fact that lipidized antibodies can " translocate across lipid membranes and penetrate intact cells" is in Kabanov, *et al.* and, unfortunately, that teachings is directed to lipidized antibodies that are ***structurally different*** from the presently claimed lipidized proteins. As explained by Dr. Malfory Camine in his declaration, there is absolutely no teaching or suggestion in the art that the lipidized proteins of the present invention, *i.e.*, lipidized proteins, wherein the protein is covalently linked to the lipid through a carbohydrate moiety, would be capable of transvascular transport, organ uptake and intracellular localization. Again, ***both*** aspects, *i.e.*, ***both*** the functional aspect ***and*** the structural aspect, of the claimed invention ***must*** be found in the prior art.

In view of the foregoing, Applicants respectfully submit that the claimed invention is not taught or suggest by the prior art. Instead, the prior art ***teaches away*** from the claimed invention. Clearly, in view of these teachings, the claimed invention is non-obvious and, thus, patentable. Accordingly, Applicant urges the Examiner to withdraw this rejection under 35 U.S.C. § 103.

b. Rejection of Claims 1-23 over Horan, et al. in view of Bischofberger, et al. and prior art disclosed in the specification

Claims 1-8, 14, 15, 20 and 23 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Horan, *et al.* in view of Bischofberger, *et al.* and prior art disclosed in the specification (page 30, lines 12-15). During the telephonic interview with Examiner Schwadron in connection with the three related, copending patent applications (*i.e.*, U.S. Patent Applications Serial Nos. 08/483,944, 08/482,116 and the present case, *i.e.* 08/973,576), the differences between Applicant's lipidated proteins and those disclosed by Horan, *et al.* in view of Bischofberger were discussed, and it was agreed that Applicant's compounds are capable of transvascular transport, organ uptake and intracellular localization, whereas the compounds of Horan, *et al.* bind to the external surface membrane of cells or viruses and are embedded into the membrane. In addition, it was pointed out that Bischofberger, *et al.* disclose the covalent conjugation of a lipid to an *oligonucleotide*, and not the lipidization of polypeptides or antibodies. In view of the differences between Applicant's compounds and those disclosed by Horan, *et al.* in view of Bischofberger, Examiner Schwadron indicated that the § 103 (a)

obviousness rejection over Horan, *et al.* in view of Bishchofberger would be overcome if the claims were, in fact, limited to lipidated proteins or lipidated antibodies that are capable of transvascular transport, organ uptake or intracellular localization.

As explained above, in order to expedite prosecution of the present case, claims 1, 9, 14, 19, and 20 have been amended to more specifically recite that the lipidized protein (claims 1 and 14) or the lipidized antibody (claims 9, 19 and 20) is capable of transvascular transport, organ uptake or intracellular localization. In view of the amendment to claims 1, 24 and 29 and, in turn, claims 2-12, 30, 32 and 33, the Examiner's concern has been overcome. Accordingly, Applicant urges the Examiner to withdraw the rejection under 35 U.S.C. § 103(a) over Horan, *et al.* in view of Bischofberger.

REJECTION UNDER 35 U.S.C § 102(E):

Claims 1-3, 7, 8, 14, 15, 19, 20 and 23 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Horan, *et al.* (U.S. Patent No. 5,665,328). During the telephonic interview with Examiner Schwadron in connection with the three related, copending patent applications (*i.e.*, U.S. Patent Applications Serial Nos. 08/483,944, 08/482,116 and the present case, *i.e.* 08/973,576), the difference between Applicant's lipidated proteins and those disclosed by Horan, *et al.* were discussed, and it was agreed that Applicant's compounds are capable of transvascular transport, organ uptake and intracellular localization, whereas the compounds of Horan, *et al.* bind to the external surface membrane of cells or viruses and are embedded into the membrane. In view of the differences between Applicant's compounds and the compounds of Horan, *et al.*, Examiner Schwadron indicated that the § 102(e) anticipation rejection over Horan, *et al.* would be overcome if the claims were, in fact, limited to lipidated proteins or lipidated antibodies that are capable of transvascular transport, organ uptake and intracellular localization.

As such, in order to expedite prosecution of the present case, claims 1, 9, 14, 19, and 20 have been amended to more specifically recite that the lipidized protein (claims 1 and 14) or the lipidized antibody (claims 9, 19 and 20) is capable of transvascular transport, organ uptake or intracellular localization. In view of the amendment to claims 1, 9, 14, 19 and 20 and, in turn, claims 2-8, 10-13, 15-18 and 21, the Examiner's concern has been overcome.

Accordingly, Applicant urges the Examiner to withdraw the rejection under 35 U.S.C. § 102(e) over Horan, *et al.*

REJECTION UNDER 35 U.S.C § 102(B):

Claims 1-23 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Malfroy-Camine (WO 94/01131).

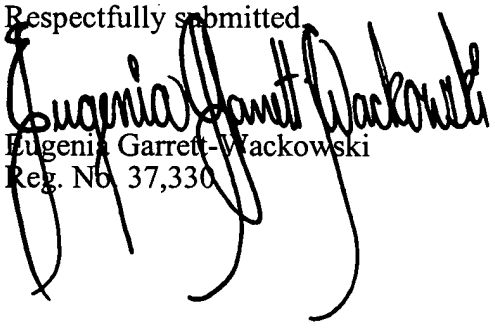
As explained above, Applicant has filed concurrently herewith a substitute declaration by the inventor that claims priority to copending U.S. Patent Application Serial No. 08/482,116, filed June 7, 1995, and U.S. Patent Application Serial No. 07/912,453, filed June 13, 1992, now abandoned. In view of the substitute declaration that claims priority back to June 13, 1992, the § 102(b) rejection of claims 1-23 is rendered moot. Accordingly, Applicant urges the Examiner to withdraw the rejection under 35 U.S.C. § 102(b) over Malfroy-Camine.

CONCLUSION

In view of the foregoing, Applicant believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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